Abstract

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Project Title: Identification of Molecular Probes that Reverse MRP-Mediated Drug Resistance

Abstract: DESCRIPTION (provided by applicant): Drug resistance, whether intrinsic or acquired, is a major clinical obstacle that contributes to the marginal efficacy of cancer chemotherapy. Multi-drug resistance (MDR) is a phenomenon by which tumor cells display or develop resistance to a number of structurally and functionally distinct anticancer drugs. A significant factor that contributes to MDR is the overexpression of certain ATP-dependent transporter proteins in tumor cell membranes that cause the efflux of cytotoxic drugs; thereby reducing their intracellular concentration and limiting their effectiveness to inhibit tumor cell proliferation and induce apoptosis. The most well characterized transport proteins responsible for MDR are the P-glycoprotein (P-gp) and the multidrug resistance protein (MRP). Inhibition of membrane transporters is an attractive therapeutic strategy to enhance chemotherapy efficacy with minimal additional toxicity. P-gp has been well studied for the past two decades and a number of inhibitors have been evaluated in clinical trials. However, none have received FDA approval due mostly to excessive toxicity when combined with chemotherapy, which is believed to be caused by the protection of normal cells and interference with drug metabolism and elimination. By comparison, less is known regarding the binding and transport properties of MRP and few inhibitors have been identified. Nonetheless, recent studies suggest that it is feasible to reverse MDR by inhibiting MRP without causing cytotoxicity. Given the potential to enhance chemotherapy with minimal additional toxicity and lack of available inhibitors, there is an urgent need to screen a large chemical library of structurally diverse compounds to identify novel MRP inhibitors using a simple cell-based model of drug resistance. The purpose of this proposal is to access the HTS resources of the Molecular Libraries Screening Center Network (MLSCN) with the goal of identifying molecular probes that can reverse MRP-mediated drug resistance. We propose a fluorescence-based cytotoxicity assay involving a MRP over-expressing human small cell lung tumor line, H69/AR. We have devised an innovative screening strategy to identify noncytotoxic, selective and potent MRP inhibitors. The availability of novel MRP inhibitors is anticipated to provide valuable tools to the scientific community that will encourage further study of MRP as a potential drug target. In addition, the resulting structure-activity analysis may help to define key topological features of inhibitors to allow for the development of a pharmacophore model. Our future plans are to identify specific chemical classes of inhibitors that have potential safety advantages, which we intend to evaluate efficacy using in vitro and in vivo models. In summary, this project is anticipated to lead to the discovery of potent and selective MRP inhibitors that can reverse resistance to chemotherapy with minimal additional toxicity.

Thesaurus Terms:
High throughput screening, Drug resistance, cancer chemotherapy, Multi-drug resistance, MDR, ATP-dependent transporter proteins, cytotoxic drugs, apoptosis, P-glycoprotein, P-gp, MLSCN, fluorescence-based cytotoxicity assay, H69/AR, noncytotoxic MRP inhibitors, pharmacophore model

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